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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/934,367	09/19/97	NEEDLEMAN P	MON-103.0-(6

EXAMINER

HM22/0131

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ART UNIT	PAPER NUMBER
1642	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/934,367	
Examiner	Group Art Unit
	1642

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 (MONTH(S)) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 07/24/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-11, 15-31 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☐ Claim(s)____ is/are allowed.

☒ Claim(s) 1-11, 15-31 is/are rejected.

☐ Claim(s)____ is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received:____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s).____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other____

Office Action Summary

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-11, 15-31 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 101, DOUBLE PATENTING

Rejection of claims 1-11, 15, 16, 22-31 pertaining to obviousness-type double patenting over co-pending applications Nos: 08/785977 and 08/788882 in view of Felgner et al, PN=5,580,859 remains for reasons already of record in paper No.12.

Applicant argues that the issue of double patenting is not ripe for this application, because this application can be allowed upon withdraw of this rejection, and because the applications Nos: 08/785977 and 08/788882 are not close to being in condition for allowance or near to issuing as a patent.

Applicant's arguments set forth in paper No.16 have been considered but are not deemed to be persuasive for the following reasons:

The instant application is not in condition for allowance. Further, even if the instant application is in condition for allowance, the double patenting issue has to be resolved before allowance.

OBJECTION

Claims 22, 23, 28 and 31 are objected to because "one or more immunogenic polypeptides" are not in the plural forms.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

1. Claims 3-11, 15-16, 23-27 are indefinite, because in claim 3 the language "thereby reducing the HDL concentration" in step (b) is contradictory to the preamble statement of the claim, which is a process for increasing the concentration of HDL concentration.

2. Claims 6, 8-11, 15 and 24 are indefinite, because there is no longer antecedent basis in claims 6, 8, 10-11 and 15 for "said immunogenic polypeptide" previously recited in claim 3.

3. Claim 2 is confusing because it is not clear whether the CETP in the blood of claim 2 refers to endogenous CETP or recombinantly expressed CETP.

4. Claims 1-11, 15-28 are indefinite because claims 1 and 3 recite a recombinant DNA molecule which is dissolved or dispersed in a vehicle. It is not clear how individual nucleotides could be dissolved or dispersed in a vehicle.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

1. Claims 1, 3, 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3, 17 are drawn to 1) an inoculum comprising a recombinant DNA molecule encoding a CETP immunogen comprising an antigenic carrier covalently bonded to one or "more" immunogenic polypeptides, comprising CETP amino acid sequence of about 10 to about 30 residues, and 2) a process for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal, or a process for producing antibodies to CETP, comprising immunizing an animal with said inoculum.

The specification discloses a CETP fragment conjugated to an antigenic carrier. The specification does not disclose nor contemplate making a conjugate of more than one CETP fragment, e.g. two or three CETP fragments, conjugated to one antigenic carrier.

2. Claims 3-11, 15-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-11, 15-27 are a process for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal, wherein the antibodies produced that bind to CETP reduce the HDL concentration.

The specification does not disclose nor contemplate that antibodies produced in a vaccinated individual, that bind specifically to CETP reduce the HDL cholesterol.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 1-11, 15-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-11, 15-16, 23-27 are drawn to 1) a process for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal, by immunizing with a recombinant DNA molecule encoding an immunogen cholesteryl ester transfer protein (CETP), which is linked to a promoter sequence that controls the expression of said CETP immunogen, said CETP immunogen comprising an antigenic carrier covalently bonded to one or more immunogenic polypeptides comprising CETP amino acid sequence of about 10 to about 30 residues. Claims 17-21, 28-31 are drawn to said immunogen recombinant DNA molecule, or an inoculum comprising said recombinant DNA molecule encoding an immunogen cholesteryl ester

transfer protein (CETP) . Claims 1, 22 are drawn to a process for producing antibodies to CETP, comprising immunizing an animal with said inoculum. Claims 1, 22 read on a a process for producing an adequate amount of antibodies to CETP to inhibit CETP activity, and therefore, increasing the concentration of HDL in blood. Claims 17-21, 28-31 read on an "inoculum", or an "immunogen" DNA sequence, as a vaccine, that produce an adequate amount of antibodies to CETP to inhibit CEPT activity, and therefore, increasing the concentration of HDL in blood.

It is unpredictable that the claimed method would significantly increase the concentration of HDL, by immunizing with a cDNA sequence encoding a CETP fragment of 10 to 30 residues, or of SEQ ID Nos: 2-13, 29, 32-37, 50, conjugated to an antigenic carrier. The specification discloses in table 1 that the p value for HDL level after injection of recombinant human CETP (rhCETP), or C-terminal 26 rabbit CETP amino acids conjugated to an antigenic carrier, thyroglobulin (CETP-TH) is 0.17 and 0.38, respectively, as compared to the control. It is well known in the art that a p value from a Student's T test should be less or equal to 0.05 to significant. In other words, the 10 percent difference seen in table 1 is due to variation within samples, rather than to a significant difference in HDL between the control and the animals immunized with recombinant human CETP, or with C-terminal 26 rabbit CETP conjugated to thyroglobulin. One of skill in the art would not have expected that immunization with a DNA sequence encoding a CETP fragment conjugated to an antigenic carrier protein would significantly increase the level of HDL, because immunization with a construct of CETP conjugated to thyroglobulin, does not significantly increase the level of HDL, and because

applicant does not disclose any working example wherein immunization with a DNA sequence encoding a CETP fragment conjugated to an antigenic carrier would significantly increase the level of HDL. Further, because it is not clear whether the claimed method would significantly increase the concentration of HDL, it is equally not clear whether the claimed method would produce a suffficient amount of antibodies to inhibit CETP activity, and therefore, increasing the concentration of HDL in blood. For the same reasons, it is not clear whether the claimed inoculum would produce an adequate amount of antibodies to CETP to inhibit CEPT activity, and therefore, increasing the concentration of HDL in blood. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. In the event that Applicant could overcome the above 112, first paragraph rejection, claims 1-11, 16-31 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of SEQ ID No: 4, 10, 29, 34 or 50, and a process of use of said DNA sequence for producing antibodies, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal, does not reasonably provide enablement for a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of about 10 to about 30 residues, or of SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37, and a process of use of said DNA sequence for

producing antibodies, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-11, 16-31 are drawn to a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of about 10 to about 30 residues, or of SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37, and a process of use of said DNA sequence for producing antibodies, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal.

The specification discloses that it is known in the art that an antagonist antibody, TP2, binds to an epitope located between about amino acid positions 465 and 475 of the 26 amino acids C-terminal region of human CETP (specification, pages 23, last paragraph bridging page 24), Hessler, B et al, 1988, JBC, 263(11): 5020-5023, IDS# A18, and Tall, 1993, J Lipid Res, 34: 1255-1274, especially p.1261, IDS#A20). That is antibody TP2 binds to the amino acid sequence Glu-His-Leu-Leu-Val-Asp-Phe-Leu-Gln-Ser-Leu. Hessler et al, *supra*, also discloses two other inhibitory antibodies, one binding to the amino acid positions 129-164, which is in the middle of CETP, and the other binding to the amino acid positions 1-15, which is at the N terminus of CETP (page 14320 and table 1). Said N-terminus peptide sequence is Cys-Ser-Lys-Gly-Thr-Ser-His-Glu-Ala-Gly-Ile-Val-Cys-Arg-Ileu. The claimed SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37 however do not comprise any sequences of the above C-terminal, or N-terminal, or middle region

disclosed by the art. The specification also discloses the intention of making antagonist antibodies specific for CETP to inhibit the activity of CETP.

One cannot extrapolate the teaching of the specification to the claims because although the specification and the art teach that there are specific regions of CETP that are antigenic and could produce antagonist antibodies, other regions of CETP, from 10 to 30 amino acids, or SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37 are not necessary immunogenic and could produce antibodies that could inhibit the activity of CETP, because not any peptides of 10 to 30 amino acids are involved in the biological activity of CETP, and because the specification does not disclose that SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37 are necessary for the activity of CETP. Further, even if the sequences of SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37 are necessary for the activity of CETP, there is no way to determine whether the antibodies produced actually bind to CETP, because it is well known in the art that using synthetic amino acid sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is, nor how immunogenic it is. Furthermore, this does not take into account the 3-dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens encoded by an isolated mammalian nucleic acid molecule therefore, cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. In the event that Applicant could overcome the above 112, first paragraph rejection, claims 1-11, 15-28 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing antibodies, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal comprising administering a recombinant DNA molecule comprising a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide, does not reasonably provide enablement for a process for producing antibodies, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal comprising administering an inoculum containing a vehicle in which is "dissolved or dispersed" a recombinant DNA molecule comprising a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-11, 15-28 are drawn to a process for producing antibodies specific for CETP, or for increasing the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal comprising administering an inoculum containing a vehicle in which is "dissolved or dispersed" a recombinant DNA molecule comprising a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide.

It is noted that a recombinant DNA molecule which is "dissolved or dispersed" in a vehicle comprises small fragments or even individual nucleotides of said DNA in a vehicle. It is not clear

how administration of said nucleotides, or fragment would produce antibodies specific for CETP or increase the concentration of high density lipoprotein (HDL) cholesterol in blood of a mammal. In view of the above, undue experimentation would be required to practice the claimed invention.

REJECTION UNDER 35 USC 102, NEW REJECTION

Claims 17, 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Jeong, NW et al, 1994, IDS# A26.

Claims 17, 29 are drawn to a DNA sequence encoding CETP immunogen comprising an antigenic carrier or exogenous antigenic carrier, covalently bonded to one or more immunogenic CETP polypeptide of about 10 to "about" 30 residues, wherein said DNA sequence is linked to a promoter sequence that controls the expression of said CETP immunogen DNA sequence. Said DNA molecule is dissolved or dispersed in a vehicle.

Jeong et al teach subcloning of a cDNA sequence encoding the carboxy terminus of CETP into a plasmid, pGEX, for the production of glutathione-CETP fusion protein. Said C-terminal peptide has 31 amino acids (p.533, second paragraph).

It is well known in the art that an expression vector contains a promoter sequence for expressing a protein. Further, 31 amino acids are the same as "about" 30 residues. Moreover, the specification defines "carrier" or "exogenous antigenic carrier" as a molecule foreign to the immunized mammal that provides a signal to antibody-producing B cells (p.14). Thus glutathione is inherently a carrier, since glutathione would be a foreign molecule to the immunized mammal,

such as human, and since it is well known in the art that any foreign molecule would provide a signal to antibody-producing B cells. Although Jeong et al do not teach that the cloned CETP cDNA fragment is dissolved or dispersed in a vehicle, it is well known in the art that plasmid vectors are in a buffer, which is a vehicle.

Thus, the claimed inoculum, or recombinant DNA molecule, appears to be the same as the prior art cDNA molecule cloned in a plasmid, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

REJECTION UNDER 35 USC 103, NEW REJECTION

1. Claims 18-21, 29 and 30 are rejected under 35 USC 103 as being obvious over Jeong et al, *supra*, in view of PN=5,650,298.

Claims 18-21, 29, 30 are drawn to a DNA sequence encoding CETP immunogen comprising an antigenic carrier or exogenous antigenic carrier, covalently bonded to one or more immunogenic CETP polypeptide of about 10 to "about" 30 residues, wherein said DNA sequence is linked to a promoter sequence that controls the expression of said CETP immunogen DNA

sequence. Said promoter is a cytomegalovirus immediate-early promoter sequence. The concentration of said DNA sequence is about 0.05 ug/ml to about 20 mg/ml. Said DNA sequence is in phosphate buffer saline, or in isotonic sucrose or is complexed with liposomes.

The teaching of Jeong et al has been set forth. Jeong et al teach subcloning of a cDNA sequence encoding the carboxy terminus of CETP into a plasmid, pGEX, for the production of glutathione-CETP fusion protein. Said C-terminal peptide has 31 amino acids (p.533, second paragraph).

Jeong et al however do not teach using a promoter which is a cytomegalovirus immediate-early promoter sequence. Jeong et do not teach that the concentration of the DNA sequence is about 0.05 ug/ml to about 20 mg/ml, and that the DNA sequence is in phosphate buffer saline, or in isotonic sucrose or is complexed with liposomes.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a promoter which is a cytomegalovirus immediate-early promoter sequence, as taught by PN=5,650,298, for expressing the carboxy terminus of CETP as taught by Jeong et al, because said promoter is commonly used in the art. Further it would have been obvious to store the DNA taught by Jeong et al in phosphate buffer saline, or in isotonic sucrose, because phosphate buffer saline, or isotonic sucrose are commonly used to store DNA. With regards to the amounts of DNA recited in claim 18, to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425. One of ordinary skill in the art would have been motivated to make a DNA sequence comprising an

antigenic carrier, covalently bonded to an immunogenic CETP polypeptide with a reasonable expectation of success

2. Claims 1, 2, and 22 are rejected under 35 USC 103 as being obvious over Jeong et al, *supra*, in view of Felgner et al (of record), further in view of Silversides, DW et al, 1988, J reproductive Immunol, 14(1): 47-58.

Claims 1, 2, and 22 are drawn to a process for producing antibodies comprising administering a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of about 10 to about 30 residues.

The teaching of Jeong et al has been set forth. Jeong et al teach subcloning of a cDNA sequence encoding the carboxy terminus of CETP into a plasmid, pGEX, for the production of glutathione-CETP fusion protein. Said C-terminal peptide has 31 amino acids (p.533, second paragraph). Jeong et al further teach that the peptides from the C-terminal region of CETP could produce antibodies against CETP (p.533).

Jeong et al however do not teach a process for producing antibodies comprising administering a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of about 10 to about 30 residues. Jeong et al do not specifically teach conjugation of an antigenic carrier to the CETP peptide.

Felgner et al teach that there are several advantages to elicit peptide specific antibodies by direct administration of the exogenous DNA, which is then expressed, rather than by

administration of the peptide itself. The advantages include avoidance of anaphylactic reaction, sustained exposure etc...

Silversides et al teach antigenic carriers conjugated to peptides to produce immune response against the peptides.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the DNA sequence taught by Jeong et al for producing antibodies against CETP, because there are advantages of using exogenous DNA for producing antibodies, as compared to administration of the peptide itself, as taught by Felgner et al, and because peptides from the C-terminal region of CETP could produce antibodies against CETP, as taught by Jeong et al. It would have been obvious to make a DNA sequence encoding the CETP peptide, as taught by Jeong et al, which is conjugated to an antigenic carrier, because it is well known in the art that an antigenic carrier would enhance the immunogenecity of a peptide, and is commonly used in the art, as taught by Silversides et al. One of ordinary of skill in the art would have been motivated to administer a DNA sequence encoding CETP immunogen comprising an antigenic carrier covalently bonded to a CETP peptide of about 10 to about 30 residues, with a reasonable expectation of success in producing antibodies against CETP.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The

examiner can normally be reached on Monday-Friday from 10:00 am to 2:00 pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

December 10, 2000